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Sleep disturbances in long-term immigrants with chronic mountain sickness: A comparison with healthy immigrants at high altitude

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ABSTRACT

The aim of this study was to examine sleep disturbances in patients with chronic mountain sickness (CMS). The sleep of 14 patients with CMS and 11 healthy controls with or without sleep disorders (control N: without sleep disorders; control D: with sleep disorders) was studied by polysomnography. Hypopnea was the sleep disorder most commonly suffered by CMS patients and control D subjects. No major differences were observed in sleep structure between CMS and control groups, with the exception of shorter rapid eye movement latency in controls and increased deep non-rapid eye movement in the control N group. Periodic breathing was observed in only two study participants, one each in the CMS and control D groups. The level of saturated oxygen was significantly lower in the CMS group during sleep than the control groups ($P < 0.05$). CMS scores were positively correlated with the apnea–hypopnea index, and negatively correlated with saturated oxygen levels. These results demonstrate that sleep disorders and nocturnal hypoxia are important in the development of CMS.

1. Introduction

Chronic mountain sickness (CMS) is a clinical syndrome that occurs at elevations above 2500 m and affects both natives and immigrants who reside at high elevations for extended periods of time. The main characteristic of this disease is a hemoglobin concentration greater than 21 g/dL for males or 19 g/dL for females. A diagnosis of CMS excludes chronic pulmonary disease or other conditions causing erythrocytosis and must include three of the following additional symptoms: breathlessness, palpitations, sleep disturbance, cyanosis, dilatation of veins, paresthesia, and headache (León-Velarde et al., 2005). Whereas the clinical characterization of CMS has been extensively detailed, the fundamental pathophysiologic process responsible for its development remains unclear.

Progression to a high altitude, especially in a short period of time, results in sleep-related breathing disorders and sleep architecture alterations (Goldenberg et al., 1992; Joern et al., 1970; Mizuno et al., 2005). These alterations are accompanied by frequent awakenings that are associated with pronounced oxygen desaturation, periodic breathing (PB), increased light non-rapid eye movement (NREM; sleep stages 1 and 2) sleep, and reduced deep NREM sleep (stages 3 and 4) (Panjwani et al., 2007). Nocturnal hypoxia and sleep disorders are also present in acute mountain sickness (Burgess et al., 2004; Erba et al., 2004; Nussbaumer-Ochsner et al., 2012a).

Although the sleep patterns of high-altitude natives and immigrants have previously been examined, the results are conflicting. Arai et al. (2002) reported that increased age in high-altitude Sherpa residents is associated with sleep desaturation. Coote et al. (1993) showed that the amount of slow wave rapid eye movement (REM) sleep of Peruvians living at 4300 m was similar to lowlanders, but they experienced episodes of PB and respiratory apneas that resulted in marked arterial desaturation. Sun et al. (1996) showed that disordered-breathing during sleep occurs with an equal, low frequency in young Tibetan and Han men. Plywaczewski et al. (2003) used a hypobaric chamber to simulate altitudes of up to 5000 m and showed that Tibetans had more episodes of PB, higher arterial oxygen saturation (SaO_2), and better sleep structure than Hans.

Only a few studies have examined the relationship between CMS and sleep architecture, with conflicting results. Spicuzza et al. (2004) found that Andean natives with excessive erythrocytosis (EE) had lower nighttime SaO_2 than controls and spent more time

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with SaO_2 < 80%, but no differences in the number and duration of apneas and hypopnoeas. Julian et al. (2013) compared the sleep of young males with EE and healthy controls in La Paz, Bolivia. They found that compared to controls, EE cases had a greater apnea–hypopnea index (AHI), a higher frequency of apneas (central and obstructive) and hypopnea during REM sleep, and lower nocturnal SaO_2.

Compared to Tibetan natives, Han Chinese show poor acclimatization to high altitude (Wu, 2004) and CMS is more common in immigrant Hans than indigenous Tibetans (Wu, 2005). However, the factors that predispose some immigrants to develop CMS are not well understood. In particular, it is unclear whether healthy immigrants residing at a high altitude for long periods of time suffer from sleep disturbances, whether there are differences in sleep disorders between immigrants that are healthy or have CMS, and to what extent these sleep disturbances correlate with CMS. In this study we tested the sleep structure, sleep-related breathing disorders, and nocturnal SaO_2 in immigrants with CMS and healthy controls residing at high elevations for long period of time.

2. Materials and methods

2.1. Subjects

The ethics committee of Qinghai University Medical College approved this study and informed consent was obtained from all subjects. This study was performed in the Yushu state of Qinghai province, China, at an altitude of 3780 m, from May 13 to July 13, 2012. Enrolled study subjects were ethnic Hans who had previously immigrated to a high altitude from the lower elevation plateau. All patients in this study had been living at a high altitude >5 year and had not ventured into the lower elevation plateau during the previous year. Immigrants were divided into CMS ($n = 14$) or control ($n = 11$) groups. The CMS group consisted of immigrants who were diagnosed with CMS (CMS score > 5) according to criteria from the consensus statement on chronic and subacute high altitude diseases (León-Velarde et al., 2005). Subjects in the control group had hemoglobin levels < 21 g/dL and a CMS score < 5. The control group was further subdivided, depending on whether the control patients suffered from sleep disturbances. Control subjects with an AHI ≥ 5 suffered from sleep disturbances and were placed in control group D. Control subjects with an AHI < 5 did not suffer from sleep disturbances and were placed in control group N. None of the study subjects had chronic obstructive pulmonary disease, chronic cor pulmonale, secondary erythrocytosis, or nervous system diseases.

2.2. CMS diagnosis and lung function

CMS was diagnosed according to the 2004 consensus statement on chronic and subacute high-altitude diseases (León-Velarde et al., 2005). Lung function in each patient was accessed by spirometry and flow-volume curves using a SpiroPro spirometer (Jaeger/Cardinal Health, Hoechberg, Germany). The pneumotachygraph was calibrated using a calibration syringe of known air volume.

2.3. Sleep study

Polysomnography (Somnomedics, Randersacker, Germany) was performed over the course of a full night of sleep and the following parameters were recorded from each patient: two electroencephalograms (two channels); two electrooculograms (left and right); chin electromyogram; nasal and mouth pressure air flow, thermal air flow; rib cage and abdominal movements; pulse oximetry; three lead electrocardiograms; oxyhemoglobin saturation using a finger probe; and body position measurements. Sleep studies were analyzed in 30 s epochs by two experienced polysomnograph technologists, following the American Academy of Sleep Medicine manual for the scoring of sleep and associated events and as the diagnosis standard (Iber et al., 2007).

The sleep parameters measured and analyzed were: total sleep time (TST); sleep efficiency (percentage of recording time spent asleep); percentage of TST that subjects spent in each sleep stage; arousal indices (arousals due to PB or upper airway obstruction, as well as spontaneous and total arousals); latency to sleep; and latency to REM sleep. An apnea was scored when airflow ceased for ≥10 s. A hypopnea was scored when the airflow was <30% of baseline for 10 s or longer and desaturation ≥4% from pre-event baseline. A central apnea was scored when there was a cessation of airflow and absent inspiratory effort. Obstructive apneas were scored when there was a cessation of airflow that was associated with continued or increased inspiratory effort. A mixed apnea was scored when there was a cessation of airflow that was associated with absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event. PB was scored when five or more central apneas or hypopneas per hour of sleep occurred and was accompanied by ≥10 consecutive min of a cyclic crescendo and decrescendo change in breathing amplitude.

2.4. Statistical analysis

Statistics were carried out using SPSS 19.0 software (IBM Corp., Armonk, NY, USA). Differences among groups were analyzed using one-way analyses of variance or the Kruskal–Wallis H-test. A Pearson's correlation coefficient was used to assess correlations between parameters. Data are presented as mean ± standard error or as median (lower quartile, upper quartile); a $P < 0.05$ was considered as statistically significant.

3. Results

The patients' histories and physical characteristics of enrolled subjects were recorded. No significant differences were observed between the CMS and either control group with respect to age, body mass index, length of time living in a plateau, or lung function (Table 1).

3.1. Sleep variables

The mean TST of both groups was >400 min and the sleep efficiency was >80%. No significant differences were observed between the CMS patients and either control group with regard to TST, sleep efficiency, NREM sleep (stages 1, 2, 3, or 4), length of REM sleep, or the arousal index (Table 2). The percentage of sleep time spent in deep NREM sleep (stage 3 and 4) was significantly lower in the CMS and control D groups compared to the control N group (Ps < 0.05), whereas the latencies to NREM stage 1 and 2 and deep NREM sleep did not differ. REM latency was significantly lower in the control groups compared to the CMS group ($P = 0.018$). Finally, REM latency in the control N group was lower than in the control D group.

3.2. Respiratory variables

The AHI and hypopnea index in the CMS and control D groups were significantly higher than in the control N group (Ps < 0.01); there was no significant difference between the CMS and control D groups. Hypopnea was the most prevalent type of sleep disorder in both the CMS and control D groups. No significant differences in the central, obstructive, or mixed apnea indices were observed among the groups. In most cases, subjects presented with central apnea and hypopnea, whereas a fewer number of cases presented

Table 1
General characteristic of the subjects.

Variable	CMS ($n=14$)	Controls D ($n=4$)	Controls N ($n=7$)	F-value	P-value
Age (years)	40.9 ± 7.8	42.0 ± 6.3	32.9 ± 8.3	2.93	0.074
Living plateau time (years)	17.6 ± 14.5	23.8 ± 8.5	14.9 ± 13.8	0.547	0.586
CMS score	11.9 ± 3.7*,Δ	1.8 ± 1.3	1.3 ± 1.5	39.336	0.000
Weight (kg)	70.3 ± 9.4	74.3 ± 7.1	66.3 ± 6.7	1.186	0.324
BMI (kg/m^2)	23.30 ± 2.0	24.7 ± 0.17	21.9 ± 2.1	2.745	0.086
HB (g/L)	233.4 ± 20.4*,Δ	180.8 ± 7.5	177.1 ± 12.9	31.172	0.000
Hct (%)	69. 6 ± 5.9*,Δ	54.2 ± 2.2	53.1 ± 3.9	27.901	0.000
VC (L)	3.3 ± 1.5	3.7 ± 0.4	4.1 ± 0.5	1.167	0.33
FVC (L)	3.7 ± 0.5	3.8 ± 0.4	4.1 ± 0.4	2.824	0.081
FEV1 (L/S)	3.3 ± 0.5	3.1 ± 0.2	3.6 ± 0.7	1.007	0.381

Data are presented as mean ± SEM; CMS, chronic mountain sickness; BMI, body mass index; Hb, hemoglobin; VC, vital capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in one second.
* Compared with controls D; $P<0.01$.
Δ Compared with controls N, $P<0.01$.

Table 2
Sleep variables recorded in CMS patients and healthy controls.

Variable	CMS ($n=14$)	Controls D ($n=4$)	Controls N ($n=7$)	F-value	P-value
Total sleep time (TST, min)	423.79 ± 128.95	401.8 ± 61.4	418.1 ± 73.0	0.063	0.939
Sleep efficiency (%)	87.3 ± 5.6	82.4 ±8.5	89.0 ± 4.1	1.743	0.198
NREM stage 1 (% of TST)	26.9 ± 17.0	31.4 ± 14.8	28.8 ± 14.5	0.128	0.880
NREM stage 2 (% of TST)	31.0 ± 17.0	33.6 ± 16.3	29.2 ± 14.6	0.094	0.911
Deep NREM (stage3 + 4, % of TST)	22.5 ± 10.6Δ	19.1 ± 5.6Δ	36.5 ± 17.5	3.584	0.045
REM (% of TST)	18.4 ± 9.9	18.4 ± 2.5	15.1 ± 10.9	0.306	0.739
NREM stage 1 latency (min)	9.2 ± 9.1	8.7 ± 6.6	19.3 ± 7.3	2.593	0.097
Deep NREM latency (min)	46.5 ± 24.5	64.3 ± 54.2	32.9 ± 28.5	2.593	0.097
Arousal index (1/h)	27.7 ± 10.6	15.2 ± 13.8	22.1 ± 14.0	2.967	0.072
NREM stage 2 latency (min)	28.0 (8.9, 38.6)	31.0 (19.5, 32.8)	30.0 (2.5, 37.5)	0.045▲	0.978
REM latency (min)	34.8 (8.6, 98.8)Δ	19.5 (14.7, 2.4)Δ	4.5 (0.5, 8.5)	7.993▲	0.018

Data of normal distribution are presented as mean ± SEM; data of skewed distribution are presented as [M (Q_L, Q_U)]; REM, rapid eye movement; NREM, non-rapid eye movement deep.
Δ Compared with controls N, $P<0.01$.
▲ Present X^2-value.

Table 3
Respiratory variables recorded in CMS and controls [M (Q_L, Q_U)].

Variable	CMS ($n=14$)	Controls D ($n=4$)	Controls N ($n=7$)	X^2-value	P-value
AHI TST (1/h)	15.2 (10.2, 22.6)Δ	17.2 (12.9, 18.2)Δ	3.8 (1.9, 4.5)	14.544	0.001
HI TST (1/h)	11.5 (8.1, 18.4)Δ	16.3(12.8, 17.1)Δ	3.7(1.9, 4.3)	13.336	0.001
AI TST (1/h)	0.6 (0.0, 1.8)	1.0(0.3, 1.5)	0.0(0.0, 0.4)	4.367	0.113
CAI (1/h)	0.6 (0.0, 1.6)	0.3(0.0, 0.6)	0.0 (0.0, 0.0)	4.082	0.130
OAI (1/h)	0.0 (0.0, 0.0)	0.7(0.1, 1.2)	0.0(0.0, 0.4)	3.804	0.149
MAI (1/h)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	1.761	0.415
AHI in REM (1/h)	16.3 (10.8, 29.2)Δ	12.4(11.5, 18.4)Δ	5.2(0,0 7.4)	10.457	0.005
AHI in NREM (1/h)	13.8 (7.5, 25.4)Δ	18.5 (11.8, 19.7)Δ	3.3(2.0, 3.4)	14.248	0.001
Mean apnea length in REM (s)	0.0 (0.0, 19.1)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	4.156	0.125
Mean apnea length in NREM (s)	13.8 (0.0, 19.4)	9.9 (2.5, 10.7)	0.0 (0.0, 11.0)	2.713	0.258
Mean hypopnea length in REM (s)	26.2 (20.1, 31.9)	18.7 (15.1, 19.0)	18.9(0, 29.4)	4.824	0.090
Mean hypopnea length in NREM (s)	24.1 (19.6, 27.3)	19.7 (15.5, 24.2)	28.9 (16.0, 33.9)	1.796	0.407

Data are presented as [M (Q_L, Q_U)]; AHI, apnea/hypopnea index; AI, apnea index; HI, hypopnea index; CAI, central apnea index; OAI, obstructive apnea index; MAI, mixed apnea index.
Δ Compared with controls N, $P<0.01$.

obstructive apnea and hypopnea or mixed apnea and hypopnea. Lastly, there were no significant differences among the three groups in mean apnea and hypopnea time, REM or NREM sleep (Table 3).

3.3. PB

Two cases of PB were observed, one in the CMS group and the other in the control D group. The percentage of TST spent in PB was 16.6% in the CMS patient and 22.1% in the control D subject, with mean PB cycle durations of 25.6 and 18.6 s, respectively. As compared to control D subject, the CMS patient had a decreased mean SaO_2 (86.7 *vs.* 79.2%) (Fig. 1).

3.4. SaO_2 measurement

During periods of wakefulness, SaO_2 was significantly lower in the CMS group than in the two control groups (all Ps < 0.01). All groups displayed decreased mean sleep SaO_2, as compared to wakeful SaO_2 ($P<0.05$). The mean sleep SaO_2 was significantly lower in the CMS group compared to the control groups (Ps < 0.01). The lowest sleep SaO_2 in the CMS and control D groups were significantly lower than in the control N group (Ps < 0.05). The CMS and control D groups also had significantly higher oxygen desaturation index, and maximum and mean oxygen reductions than in the control N group (Ps < 0.01). No significant differences were seen in these three indices between CMS patients and the control D group.

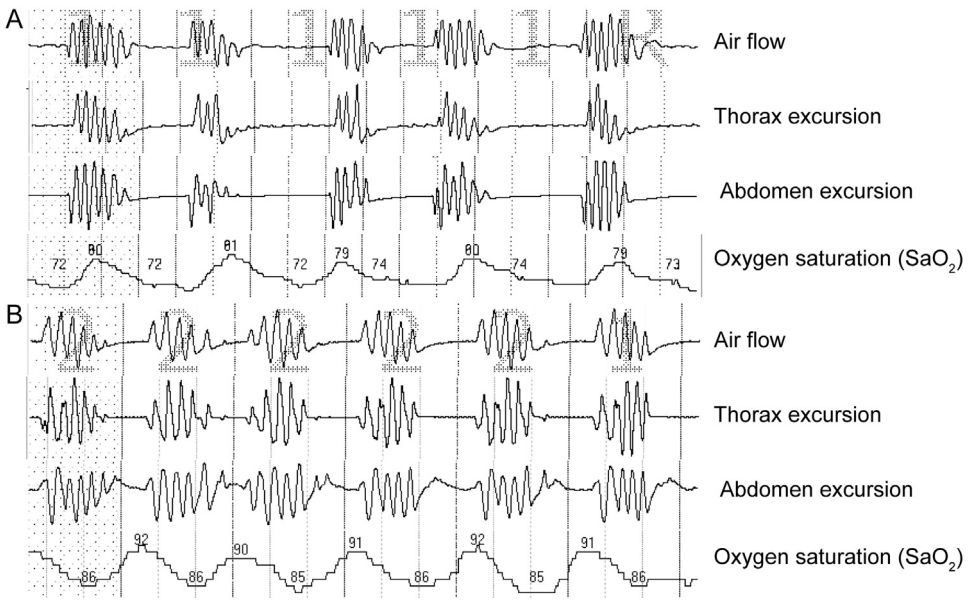

Fig. 1. Periodic breathing (PB). (A) Chronic mountain sickness patient; (B) Control D subject.

The time spent at various SaO_2 levels during sleep was also recorded. CMS patients and the control D subjects spent significantly more time during sleep with $SaO_2 < 90\%$ than the control N subjects (Table 4). CMS patients spent significantly more time during sleep with $SaO_2 < 80\%$ than the control groups ($P < 0.05$). The three study groups differed in terms of time spend at various SaO_2 levels, with much lower SaO_2 levels during the night in the CMS group (Fig. 2).

3.5. Correlations of CMS scores and measured sleep parameters

Pearson correlation coefficients were used to determine the correlation between CMS score and recorded sleep parameters (Fig. 3). This analysis demonstrated that CMS scores were positively correlated with AHI ($r = 0.400$; $P = 0.048$) and time of $SaO_2 < 80\%$ ($r = 0.577$; $P = 0.003$), and negatively correlated with mean sleep SaO_2 ($r = -0.592$; $P = 0.002$), lowest sleep SaO_2 ($r = -0.617$; $P = 0.001$) and awake SaO_2 ($r = -0.752$; $P = 0.001$).

4. Discussion

A few studies (Berssenbrugge et al., 1983; Joern et al., 1970; Mizuno et al., 1993; Reite et al., 1975) have demonstrated that when people travel to high altitudes in a short period of time the following traits are observed: decreases in TST and sleep efficiency, increases in stage 1 sleep, and decreases in stage 2, 3,

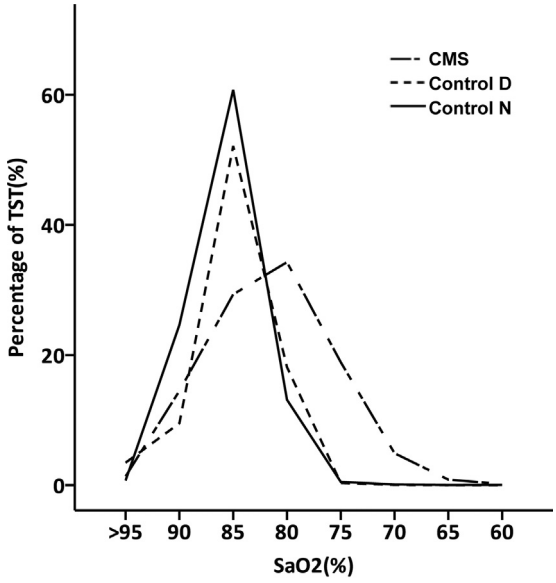

Fig. 2. Percentage of time spent in different SaO_2 ranges. Dashed lines refer to chronic mountain sickness patients, dotted lines refer to the control D group (with sleep disorders), and solid lines refer to the control N group (without sleep disorders).

Table 4
SaO_2% recorded in CMS patients and healthy controls.

Variable	CMS ($n = 14$)	Controls D ($n = 4$)	Controls N ($n = 7$)	*F*-value	*P*-value
Awake SaO_2 (%)	86.4 ± 1.0*,Δ	90.0 ± 0.8	91.3 ± 1.0	74.045	0.000
Lowest sleep SaO_2 (%)	68.5 ± 7.6Δ	71.5 ± 6.2Δ	80.3 ± 3.8	7.588	0.003
Mean sleep SaO_2 (%)	83.36 ± 4.14*,Δ	87.5 ± 1.7	87.6 ± 2.2	4.574	0.022
Times of $SaO_2 < 90\%$ (1/h)	181.3 ± 113.3Δ	177.8 ± 62.7Δ	43.3 ± 28.6	5.654	0.010
Times of $SaO_2 < 80\%$ (1/h)	72.0 ± 66.7*,Δ	6.0 ± 5.4	1.7 ± 3.4	5.533	0.011
Oxygen desaturation index (1/h)	31.6 ± 14.3Δ	33.4 ± 10.6Δ	8.3 ± 4.8	9.967	0.001
Maximum oxygen reduction (%)	13.4 ± 2.3Δ	12.3 ± 2.6	7.9 ± 1.9	15.332	0.000
Mean oxygen reduction (%)	5.7 ± 0.7Δ	5.4 ± 0.4	4.7 ± 0.3	6.914	0.005
The longest oxygen reduction time (s)	56.9 ± 25.3	59.7 ± 21.6	61.2 ± 40.3	0.053	0.948

Data are presented as mean ± SEM.
* Compared with controls D.
Δ Compared with controls N.

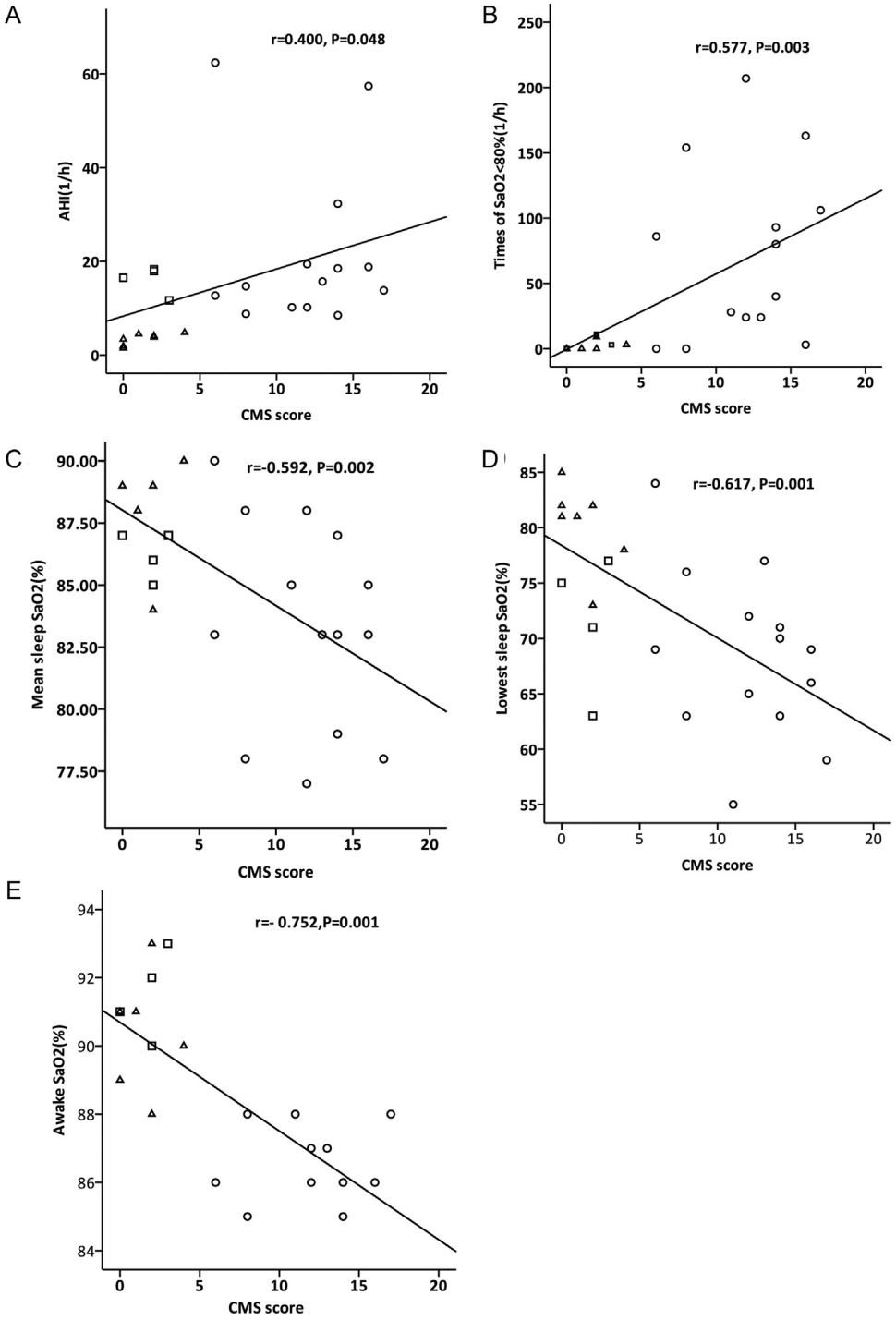

Fig. 3. Correlations of chronic mountain sickness (CMS) scores and measured parameters. (A) Apnea–hypopnea index. (B) Time spent SaO_2 < 80%. (C) Mean sleep SaO_2. (D) Lowest sleep SaO_2. (E) Awake SaO_2. Open circles (○) refer to the CMS group, squares (□) refer to the control D group (with sleep disorders), and triangles (△) refer to the control N group (without sleep disorders).

and 4 sleep. Nussbaumer-Ochsner et al. (2012b) found that sleep quality was initially impaired (decreases in sleep efficiency, SaO_2, and slow wave sleep) the first night at a high altitude (4559 m), but these factors improved by the third night, thus demonstrating an improvement in sleep quality with short-term acclimatization. The few studies evaluating sleep in long-term high-altitude residents indicate that long-term acclimatization does not impact sleep structure (Coote et al., 1993; Spicuzza et al., 2004). In contrast to these and another study (Carskadon et al., 2000), our findings identify important differences in sleep structure in native high-altitude residents, including increased NREM stage 1 sleep and decreased stage 2 sleep. Although stages 3 and 4 sleep in subjects with sleep disorders were comparable with sea level results, there were significant increases in controls without sleep disorders. Thus, the sleep patterns of immigrant Hans at high altitudes differ from people who reside at sea level, who are native residents of high altitude, or who rapidly ascend to high altitudes.

Compared to normal REM latency at sea level (70–90 min) (Carskadon et al., 2000), the REM latency was substantially shorter for all subjects in this study. The shortest latency was observed

in healthy controls without sleep disorders and longest in CMS patients. A previous study by Coote et al. (1992) found that the onset of REM sleep occurred quite early in the night in both younger and older Andean natives, and this was particularly evident in older subjects. Whether a shorter REM latency is a feature of acclimatization to high altitude remains unclear, and future studies may help to resolve this issue.

In addition to all of the CMS patients, some of the healthy control subjects suffered from sleep disorders, primarily hypopnea. The AHI did not differ between these groups, and the proportion with apnea was small. Previous studies demonstrated that while high-altitude natives display little or no sleep apnea or PB (Hackett et al., 1980; Kryger et al., 1978a,b; Lahiri et al., 1983), the majority did have various kinds of respiratory dysrhythmia, typically an undulant oscillation in depth of breathing without true apnea (Kryger et al., 1978a,b). Spicuzza et al. (2004) did not observe major sleep abnormalities in natives Andeans with or without EE. Simple and occasional hypopneas were the most predominant sleep disorder found and these disorders were equally frequent in EE and controls. These sleep results are very different than those of lowlanders who ascend to a high altitude in a short period of time.

Previously published studies indicate that PB is the phenomenon that most commonly develops in people who rapidly progress to a high altitude (Khoo et al., 1996; Masuyama et al., 1989; Zielinski et al., 2000). However, only two cases of PB were observed in our study. The importance of this finding is unclear due to paucity of reports regarding PB in CMS and long-term high-altitude residents. Lahiri and Hackett also described that Sherpas exhibited few PB episodes with apnea during sleep (Hackett et al., 1980; Lahiri et al., 1983).

Sleep-disordered breathing correlates with the hypoxic ventilatory response (HVR) at high altitude (Lahiri et al., 1983). When people ascend to a high altitude, the partial pressure of arterial oxygen decreases, the HVR increases, and the partial pressure of arterial carbon dioxide decreases. These alterations result in modifications to the chemoreflex control of breathing and changes in cerebrovascular responses causing apnea, hypopnea, and PB (Ainslie et al., 2013). However, the HVR of immigrants residing at high altitudes is blunted (Weil et al., 1971). Two previous studies found that ventilation measured in CMS patients was lower than normal during the day and night (Sun et al., 1990; Zubieta-Calleja et al., 2006). Spicuzza et al. (2004) showed that AHI was correlated not with HVR, but with the hypercapnic ventilatory response in EE and native Andeans. Slessarev et al. (2010) found that both highlanders and acclimatized lowlanders exhibit blunted peripheral carbon dioxide chemosensitivity and respond to hypoxia with a decrease in ventilatory recruitment threshold. There are studies showing that after using ventilatory stimulants (medroxyprogesterone acetate and acetazolamide), HVR increased and the nocturnal hypoxia improved during sleep in long-term residents at high altitude or in CMS patients (Kryger et al., 1978a, 1978b; Richalet et al., 2005). Hypoventilation and decreased ventilatory drive may have a permissive role in respiratory dysrhythmia and hypoxemia in highlanders during sleep at a high altitude.

Polycythemia is a main characteristic of CMS, and hemoglobin concentration is positively correlated with SaO_2 (Monge-C et al., 1992; Reeves and Leon-Velarde, 2004). Hypoxia is thought to stimulate the secretion of erythropoietin and induce erythrocyte proliferation (Haase, 2013), and $SaO_2 < 80\%$ thus would trigger a greater erythropoietin release (Cohen et al., 1981). Spicuzza et al. (2004) recorded SaO_2 values $\leq 80\%$ during the entire night period in EE subjects, whereas levels remained >80% in controls. They also found a significant correlation between SaO_2 values during sleep and erythropoietin levels during the morning in native Andeans with EE (Bernardi et al., 2003). Control subjects with sleep disorders in our study had higher mean sleep SaO_2 than CMS patients and spent much less time with $SaO_2 < 80\%$ (0.4 *vs.* 24.8% TST). The reason for this is not clear, however, there may be a genetic component, as has been reported for CMS (Zhou et al., 2013) and acute mountain sickness (Buroker et al., 2012; MacInnis et al., 2010). Our results show that CMS score positively correlates with time of $SaO_2 < 80\%$ and AHI, and negatively correlates with SaO_2 levels, suggesting that lower SaO_2 during the night plays an important role in the development of CMS in long-term immigrant Hans.

The main limitation of this study was the limited number of subjects. The low population density at high altitudes and the small number of people qualifying for study inclusion reduced the number of subjects available for study enrollment. Thus, future studies with larger sample sizes are needed to confirm this research.

In conclusion, this study provides important new information concerning the sleep status of Han immigrants with or without CMS. Sleep disorders such as hypopnea and nocturnal hypoxia likely contributed to the development of CMS in these subjects. For high-altitude immigrants with sleep disorders, higher SaO_2 levels may have hindered CMS development.

Author contributions

W.G. and R.L.G. conceived of and designed this study; Q.G. and R.L. performed polysomnography; Z.Z.B. and T.W. provided statistical analysis; J.W. was responsible for identifying control subjects; Y.Z.Y. performed physical examinations on each subject; W.G. wrote the draft of this article; R.L.G. diagnosed the CMS.

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